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Remarks

Courtesies extended to Applicants' representatives during the telephone interview held on February 5, 2007, are acknowledged with appreciation.

In accordance with the present invention, there are provided novel G-protein-coupled receptor proteins which have high binding affinity for corticotropin-releasing factor (CRF), thus, such proteins are referred to as CRF-receptors (CRF-Rs). In particular, the present claims are directed to human subtypes CRF-RA_1 and a splice variant thereof containing a 29 amino acid insert, CRF-RA_2. The invention receptor is a principal neuroregulator of the hypothalamic-pituitary-adrenal cortical axis and plays an important role in coordinating the endocrine, autonomic and behavioral responses to stress and immune challenge. CRF-R is functionally coupled to adenylate cyclase as it transduces the signal for CRF-stimulated intracellular cAMP accumulation. The invention CRF-Rs or fragments thereof can be employed in a variety of ways, such as, for example, in bioassays, for production of antibodies thereto, in therapeutic compositions containing such proteins, fragments, and/or antibodies, and the like.

By the present communication, claims 1 and 11 have been amended to define Applicants' invention with greater particularity. No new matter is introduced by the subject amendments as the amended claim language is fully supported by the disclosure and the original claims. In addition, claims 3, 4, 15-18, and 20 are cancelled herein without prejudice.

Accordingly, after amending the claims as set forth above, claims 1, 2, 5-11, 13, 14, and 19 are pending in the application. A detailed listing of all claims that are, or were, in the application, irrespective of whether the claim(s) remain under examination, is presented in the Listing of Claims, beginning on page 2 of this communication, with an appropriate status identifier for each claim.

I. **Priority**

Applicants respectfully disagree with the Examiner's determination that claims making reference to SEQ ID NOs: 14 or 15 are only entitled to benefit of the priority date of the parent, 09/191,724, 12 November 1998 (Office Action, page 4).

The Examiner asserts that according to MPEP 201.11, in order for a last filed application to claim benefit of priority of the earliest filed application, there must be 1) "continuity via copendency in the chain of intervening applications" and 2) "continuity of subject matter in the chain of intervening applications" (Office Action, page 4). It is respectfully submitted that both of these requirements have been satisfied and that therefore, the claimed subject matter is entitled to a priority date of, at the latest, August 23, 1993, the filing date of earlier-filed Application No. 08/110,286 now U.S. Patent No. 5,728,545 ("the '545 patent").

With respect to the first requirement (i.e., continuity of copendency in the chain of applications), the table below shows the filing date and issue/abandonment date for each of the US patent applications and the PCT application in the priority claim.

Application No.	Filing Date	Issue/Abandonment Date
08/079,320	6/18/93	Pending at least until 7/11/94 (3 months after mailing date of final rejection)
08/110,286	8/23/93	3/17/98 (Issued - US Pat No. 5,728,545)
PCT/US94/05908	5/25/94	N/A
08/353,537	12/9/94	12/18/01 mailing date of Notice of Abandonment
08/483,139	6/7/95	1/7/02 mailing date of Notice of Abandonment
09/191,724	11/12/98	10/28/03 (Issued – US Patent No. 6,638,905)
10/649,193	8/26/03	Pending

As is readily apparent from the above table, continuity via copendency has been maintained from the filing of the earliest filed case through the present case.

With respect to the second requirement (i.e., continuity of subject matter in the chain of intervening applications), the sequences set forth in SEQ ID NO:14 and SEQ ID NO:15 are fully

supported by the disclosure of each of the earlier-filed applications going back at least as far as US Patent Application Serial No. 08/110,286 (filed August 23, 1993), now US Patent No. 5,728,545.

Specifically, SEQ ID NO:15 of the present application, an exemplary sequence of hCRF-RA_2, is a splice variant of hCRF-RA_1 that includes a 29 amino acid insert located between amino acid residues 145 and 146 of hCRF-RA_1 This sequence is fully supported by the '545 patent where the following disclosure can be found:

- sequence of SEQ ID NO:2 (amino acid sequence of hCRF-RA_1), presented at col. 31-34, is identical to SEQ ID NO:2 of the present application;
- sequence of SEQ ID NO:4 (the 29 amino acid insert), presented at col. 35, is identical to SEQ ID NO:4 of the present application; and
- the location of the 29 amino acid insert is specified at col. 28, lines 55-59, i.e., between residues 145 and 146 of hCRF-RA_1, consistent with the location specified in the present application.

Thus, SEQ ID NO:15 simply shows the sequence resulting from incorporation of SEQ ID NO:4 between residues 145 and 146 of SEQ ID NO:2. Therefore, SEQ ID NO:15 is fully supported by the disclosure of the '545 patent because all of the sequence information of SEQ ID NO:15 is represented by the sequences of SEQ ID NOs: 2 and 4 and the description of the location of the insert.

Similarly, SEQ ID NO:14 of the present application is a nucleotide sequence which encodes SEQ ID NO:15. Thus, SEQ ID NO:14 merely shows the nucleotide sequence resulting from the incorporation of the nucleotide sequence of SEQ ID NO:3 into the nucleotide sequence of SEQ ID NO:1 between nucleotides 516 and 517. SEQ ID NO:14 is fully supported by the disclosure of the '545 patent. See, for example, the following disclosure provided by the '545 patent:

- sequence of SEQ ID NO:1 (nucleotide sequence of hCRF-RA_1), presented at col. 29-32, is identical to SEQ ID NO:1 of the present application;
- sequence of SEQ ID NO:3 (the nucleotide sequence encoding the 29 amino acid insert), presented at col. 33, is identical to SEQ ID NO:3 of the present application; and
- the location of the nucleotide sequence encoding the 29 amino acid insert is specified at col. 28, lines 48-53, i.e., as between residues 516 and 517 of nucleotide sequence encoding hCRF-RA_1, consistent with the location specified in the present application.

Thus, SEQ ID NO:14 is fully supported by the disclosure of the '545 patent because all of the sequence information of SEQ ID NO:14 is represented by the sequences of SEQ ID NOs: 1 and 3 and the description of the location of the insert.

Similar disclosure can be found in each of the intervening applications between the '545 patent and the present case. The table below cites exemplary support found in each of the intervening applications:

Application No.	Support for SEQ ID NO:15	Support for SEQ ID NO:14
PCT/US94/05908	p. 60, lines 6-8; p. 60, lines 15-19; pp. 65-66; p. 67	p. 60, lines 2-5; p. 60, lines 9-14; pp. 63-65; p. 66
08/353,537	p. 68, lines 6-8; p. 68, lines 15-19; Sequence Listing	p. 68, lines 2-5; p. 68, lines 9-14; Sequence Listing
08/483,139	p. 72, lines 6-8; p. 68, lines 15-19; Sequence Listing	p. 72, lines 2-5; p. 68, lines 9-14; Sequence Listing
09/191,724 USPN 6,638,905	'905 patent col. 36, lines 63-67; columns 57-61	'905 patent col. 36, lines 57-62; columns 61-63

Thus, the continuity of subject matter with respect to sequences of SEQ ID NOs:14 and 15 has been maintained beginning with, at the latest, US Patent Application Serial No. 08/110,286 (i.e., US Patent No. 5,728,545) through all of the intervening applications up to and including the filing of the present case.

Accordingly, as all of the requirements of MPEP 201.11 have been satisfied, Applicants are entitled to a priority date of, at the latest, the filing date of the application resulting in the '545 patent: August 23, 1993.

II. Claim Rejection under 35 USC § 112, Second Paragraph

The rejection of claims 1-11 under 35 USC § 112, second paragraph as allegedly being indefinite for use of the phrase "low stringency" in claims 1 and 11 is respectfully traversed. As a preliminary matter, this rejection as applied to claims 3 and 4 has been rendered moot by the cancellation of those claims.

Specifically, Applicants disagree with the Examiner's assertion that 'low stringency' is allegedly indefinite, because "[t]he definitions in the specification and the literature of suitable, low, moderate, etc. stringency are open ended, thus the metes and bounds of the claims cannot be known" (Office Action, page 6). Contrary to the Examiner's assertion, the meaning of the phrase "low stringency" is clear when read in the context of the claim and that which is disclosed in the application and known to those of skill in the art.

The text of claim 1 further defines "low stringency" as "allow[ing] identification of sequences *having at least 50% nucleic acid identity* with respect to the reference polynucleotide sequence" (emphasis added). Thus, "low stringency" is the stringency required to achieve a specified minimum level of nucleic acid identity. Moreover, "low stringency conditions" are described at page 43, line 20 to page 44, line 13 as conditions which "allow the identification of sequences which have a substantial degree of similarity [i.e., at least 50% homology] with the probe sequence." Low stringency conditions are further described as comprising "a temperature of less than 42.5 °C, a formamide concentration of less than about 50%, and a moderate to low salt concentration." Exemplary low stringency conditions are also described.

Moreover, it is respectfully submitted that the term "low stringency" is consistent with claim language as issued in at least one other related case. The table below summarizes the

patents that have issued in this family, including all patents claiming priority to the '545 patent, and the specific claim language used with respect to "stringency" and "percent identity."

Patent No.	Claimed Subject Matter	Claim Language - Stringency	Claim Language – % Identity
5,728,545	Nucleic acid [CRF-RA_2]	"moderately stringent"	70%
6,638,905	Protein [CRF-RA_1]	"suitable stringency"	50%
6,482,608	Cell line expressing recombinant CRF-R	"low stringency" (hybridization conditions defined)	Not defined
6,399,315	Screening method	Hybridization: 50% formamide, 5X Denhart's, 5X SSPE, 0.2% SDS @ 42 °C Wash: 0.2X SSPE, 0.2% SDS @ 65 °C	Not defined
6,495,343	Nucleic acid [CRF-RB]	"moderately stringent" (conditions defined as in the '315 patent)	Not defined

As can be seen in the table above, the term "low stringency" is consistent with language previously found to be acceptable (see, for example, US Patent No. 6,482,608).

However, in efforts to reduce the issues and expedite prosecution, claim 1 has been amended herein to replace "low stringency" with "moderate stringency," which is further defined in the claim as "comprising hybridization in 50% formamide, 5X Denhart's solution, 5X SSPE, 0.2% SDS at 42 °C, followed by washing in 0.2X SSPE, 0.2% SDS, at 65 °C." It is respectfully submitted that this language is consistent with that of US Patent Nos. 6,399,315 and 6,495,343. Moreover, the minimum requirement with respect to percent identity has been amended to replace "at least 50% nucleic acid identity" with "at least 70% nucleic acid identity." This amended language is consistent with the language of the '545 patent.

Accordingly reconsideration and withdrawal of this rejection are respectfully requested.

III. Claim Rejection under 35 USC § 112, First Paragraph (Enablement)

The rejection of claims 1-6, 8-11, and 13-19 under 35 USC § 112, first paragraph as allegedly failing to meet the enablement requirement is respectfully traversed for at least the

reasons already of record. As a preliminary matter, this rejection as applied to claims 3, 4, and 15-18 has been rendered moot by the cancellation of those claims.

In particular, Applicants respectfully disagree with the Examiner's assertion that "the claims encompass a huge number of variants" (Office Action, page 10). Contrary to the Examiner's assertion the claimed variants embrace a defined group of full-length proteins that must meet certain requirements. For example, in claim 1 as currently amended, contemplated variants must (1) bind CRF and (2) be encoded by DNA that meets the following requirements:

- hybridizes to the complement of the polynucleotide sequence set forth in SEQ ID NO:14 under moderately stringent conditions, comprising hybridization in 50% formamide, 5X Denhart's solution, 5X SSPE, 0.2% SDS at 42 °C, followed by washing in 0.2X SSPE, 0.2% SDS, at 65 °C, and
- has at least 70% nucleic acid identity with respect to SEQ ID NO:14.

Thus, contemplated variants are a defined set of proteins that bind CRF and are encoded by nucleic acid sequences that are closely related to the exemplary nucleic acid sequences disclosed in the present application.

To the extent that the Examiner's assertion that the claims are allegedly "very broad" is based on claim 1 allegedly embracing fragments of CRF-Rs, it is respectfully submitted that the invention defined by claim 1 is directed to a CRF-R protein and not a fragment thereof. It is further respectfully submitted that the term "protein" is consistently used in the claims to refer to a full-length receptor having certain functional properties (e.g., claim 1). In contrast, the term "fragment" is used consistently in the claims to refer to a portion of a full length receptor (e.g., "antigenic fragment" in claim 11). Moreover, this distinction is reflected in the specification in which these terms are used consistent with the description above and are often listed separately as distinct alternatives. See, for example, the specification at p. 5, line 24 to p. 6, line 6, where the following text can be found:

> In accordance with the present invention, recombinant DNA molecules encoding CRF-Rs are also provided. DNA molecules

> encoding CRF-Rs (or fragments thereof) are useful, for example, as probes for detecting the presence of CRF-R encoding nucleic acids in biological samples, the identification of additional CRF receptor proteins, as coding sequences which can be used for the recombinant expression of the invention receptor proteins (or functional fragments thereof), and the like. Recombinant human CRF-Rs have been expressed in COS cells and bind to CRF and CRF analogs with high affinity. The recombinant production of CRF-Rs makes feasible their use in the foregoing manners.

See also p. 50, lines 17-22, where the following disclosure can be found:

> In one embodiment, a diagnostic system for assaying for the presence or quantity of CRF-R (or more likely a fragment of CRF-R) in a vascular fluid sample, such as blood, plasma, or serum, or in a tissue sample, comprises a package containing at least one CRF-R protein or polypeptide fragment thereof of this invention.

See also p. 55, lines 25-29, where the following disclosure can be found:

> Thus, in preferred embodiments, CRF-R protein, a CRF-R polypeptide fragment thereof, a polyclonal anti-CRF-R antibody, or a monoclonal anti-CRF-R antibody is affixed to a solid matrix to form a solid support that comprises a package in the subject diagnostic systems.

Thus, the claim is directed to a defined set of CRF receptor proteins satisfying specific structural and functional properties.

To the extent the rejection is based on the Office's interpretation of the claims as allegedly allowing for rehybridization under conditions whereby nucleic acids hybridize under hybridization and wash conditions less stringent than those specifically recited in the claims, this interpretation is not reasonable. Although it is the Office's obligation to give the broadest reasonable interpretation to the claims, it is improper to ignore specific requirements of the claims. To interpret the claims as embracing proteins encoded by nucleic acids that hybridize under lower stringency hybridization and wash conditions than those specifically recited in the claims, effectively ignores those requirements. In order for a protein to be embraced by the claim, that protein must meet the following requirements:

(1) bind CRF and

(2) be encoded by DNA that meets the following requirements:

- hybridizes to the complement of the polynucleotide sequence set forth in SEQ ID NO:14 under moderately stringent conditions, comprising hybridization in 50% formamide, 5X Denhart's solution, 5X SSPE, 0.2% SDS at 42 °C, followed by washing in 0.2X SSPE, 0.2% SDS, at 65 °C, and
- has at least 70% nucleic acid identity with respect to SEQ ID NO:14

It does not matter how many hybridization or wash steps are involved in obtaining that nucleic acid; embraced proteins must still meet the above requirements.

For at least the reasons above, it is respectfully submitted that Applicants have clearly set forth how to make and use the present invention as required by 35 U.S.C. § 112, first paragraph. Accordingly, reconsideration and withdrawal of this rejection under 35 U.S.C. 112, first paragraph, are respectfully requested.

IV. Claim Rejections under 35 U.S.C. § 102(b)

A. The rejection of claims 1-7, 9-13, and 15-20 under 35 U.S.C. § 102(b) as allegedly being anticipated by Laurent et al. (FEBS 335:1-5, 1993) is respectfully traversed. As a preliminary matter, the Examiner acknowledged at page 5 of the Office Action that this rejection, as applied to claim 12, had been withdrawn in response to the cancellation of the claim. Thus, the inclusion of claim 12 in this rejection as set forth on page 10 of the Office Action appears to be in error.

The publication date of the Laurent reference is November 29, 1993, the date of that issue of the FEBS journal. However, as discussed above in Section I, the subject matter of the present claims is entitled to a priority date of August 23, 1993, at the latest. Since the Laurent reference

was published after the priority date of the present application, it is not available as prior art with respect to the present claims.

Accordingly, reconsideration and withdrawal of this rejection are respectfully requested.

B. The rejection of claims 1, 8, 13, and 14 under 35 U.S.C. § 102(b) as allegedly being anticipated by Chen et al. (PNAS 90:8967-71, 1993) is respectfully traversed.

The publication date of the Chen reference is October 1, 1993, the date of that issue of the PNAS journal. However, as discussed above in Section I, the subject matter of the present claims is entitled to a priority date of August 23, 1993, at the latest. Since the Chen reference was published after the priority date of the present application, it is not available as prior art with respect to the present claims.

Accordingly, reconsideration and withdrawal of this rejection are respectfully requested.

V. Double Patenting

The rejection of claims 1-11 and 13-20 on the ground of nonstatutory obviousness-type double patenting over claims 1-8 of U.S. Patent No. 5,728,545 ("the '545 patent") is respectfully traversed.

It is respectfully submitted that the claims of the present application (directed to CRF receptor proteins) are patentably distinct from the claims of the '545 patent (directed to nucleic acids encoding CRF receptors). Indeed, the Patent Office asserted that CRF-R proteins and nucleic acids encoding CRF-R proteins are patentably distinct in issuing a Restriction Requirement during the prosecution of Application Serial No. 08/110,286 (from which the '545 patent issued; *see* Paper No. 14 (copy of the pages 1-2 provided herewith for the Examiner's convenience)). Specifically, in this Restriction Requirement claims drawn to "a receptor protein" (Group I) were restricted from claims drawn to "a DNA molecule" (Group II). Thus, the claims as filed in the present application are consistent with the grouping of claims set forth in the

Restriction Requirement in the parent case. Therefore, the rejection on the ground of nonstatutory obviousness-type double patenting is not proper.

Accordingly, reconsideration and withdrawal of this rejection are respectfully requested.

Conclusion

In view of the above amendments and remarks, prompt and favorable action on all claims is respectfully requested. In the event any matters remain to be resolved in view of this communication, the Examiner is encouraged to call the undersigned so that a prompt disposition of this application can be achieved.

Respectfully submitted,

Date: February 28, 2007

By _____

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Enclosure-- Copy of pages 1-2 of Paper No. 14 from Appln. No. 08/110,286

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SERIAL NUMBER	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/110,286	08/23/93	PERRIN	M P419439

EXAMINER	
GUEST CERMAK, S	
ART UNIT	PAPER NUMBER
1812	14

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DATE MAILED: 09/28/94

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

Response / Drawings: Dec 28 94

☒ This application has been examined ☒ Responsive to communication filed on 9/6/94 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), 0 days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☒ Notice of References Cited by Examiner, PTO-892, (5 page)
2. ☒ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☒ Claims 1-21 are pending in the application.
   Of the above, claims 1-3, 12-21 are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 4-11 are rejected.
5. ☐ Claims _____ are objected to.
6. ☒ Claims 1-21 are subject to restriction or election requirement.
7. ☒ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____, has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

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Pretty, Schroeder, Brueggemann & Clark

PTOL-326 (Rev. 2/93) EXAMINER'S ACTION

Part III DETAILED ACTION

Election/Restriction

Restriction to one of the following inventions is required under 35 U.S.C. 121:

Group I. Claims 1-3, drawn to a receptor protein , classified in class 530, subclass 350.

Group II. Claims 4-11, drawn to a DNA molecule, and a method of producing the protein, classified in class 536, subclass 23.5; class 435, subclasses 69.1.

Group III. Claim 12, drawn to an DNA hybridization assay, classified in class 435, subclass 7.6.

Group IV. Claim 13-16, 19-20, drawn to a receptor binding assay, classified in class 435, subclass 7.1.

Group V. Claims 17-18, 21 drawn to an antibody and binding assay, classified in class 530, subclass 388.22.

The inventions are distinct, each from the other because of the following reasons:

Inventions I and IV are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (M.P.E.P. § 806.05(h)). In the instant case the protein receptor can be used in a materially different process such as raising antibodies, or in a diagnostic system.